

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

REC'D 28 JUN 2004

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| Applicant's or agent's file reference CLJ/B45314 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416) | |
| International application No. PCT/EP 03/08567 | International filing date (day/month/year) 31.07.2003 | Priority date (day/month/year) 02.08.2002 |
| International Patent Classification (IPC) or both national classification and IPC A61K39/095 | | |
| Applicant GLAXOSMITHKLINE BIOLOGICALS S.A. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

I ☒ Basis of the opinion

II ☐ Priority

III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability



IV ☐ Lack of unity of invention

V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

VI ☐ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

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| Date of submission of the demand 18.02.2004 | Date of completion of this report 25.06.2004 |
| Name and mailing address of the International preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 | Authorized Officer Noë, V Telephone No. +31 70 340-4181 <div style="text-align: right;">  </div> |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/08567**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*):

Description, Pages

1-51 as originally filed

Claims, Numbers

1-71 as originally filed

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☒ furnished subsequently to this Authority in written form.
☒ furnished subsequently to this Authority in computer readable form.
☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/08567**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).
- (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 56,57,70 (with respect to IA) and 1-14,16,18,20-43,45-48,51-71 (partially)
because:
 - ☒ the said international application, or the said claims Nos. 56,57,70 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☒ no international search report has been established for the said claims Nos. 1-14,16,18,20-43,45-48,51-71 (partially)
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the Standard.
 - ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|---------------|
| Novelty (N) | Yes: Claims | 1-71 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 1-71 |
| | No: Claims | |
| Industrial applicability (IA) | Yes: Claims | 1-55,58-69,71 |
| | No: Claims | |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/08567**

2. Citations and explanations

see separate sheet

III. Non-establishment of opinion (Continuation)

Claims 56,57,70 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V. Reasoned statement (Continuation)**2.1 CITATIONS**

Reference is made to the following documents:

- D1: WO 01 09350 A (DALEMANS WILFRIED L J ;SMITHKLINE BEECHAM BIOLOG (BE); THIRY GEORG) 8 February 2001 (2001-02-08) cited in the application
- D2: WO 00 71725 A (PIZZA MARIAGRAZIA ;RAPPUOLI RINO (IT); CHIRON SPA (IT); GIULIANI M) 30 November 2000 (2000-11-30) cited in the application
- D3: WO 99 31132 A (JENNINGS MICHAEL PAUL ;PEAK IAN RICHARD ANSELM (AU); UNIV QUEENSLA) 24 June 1999 (1999-06-24) cited in the application

2.2 NOVELTY (Art. 33(2) PCT)

2.2.1 D1 discloses immunogenic compositions comprising outer membrane vesicles derived from gram negative bacteria (*Neisseria meningitidis*, *Moraxella catarrhalis*, *Haemophilus influenzae*) in which protective antigens are upregulated and non-protective antigens are downregulated and the Lipid A moiety of LPS is detoxified. The list of upregulated antigens comprises Hsf-like and transferrin binding protein. (see abstract, page 12, line 32 - page 13, line 14; page 14, line 12-22; page 20, line 11-22; page 23, line 21 - page 24, line 7; page 25, line 11 - page 27, line 22; page 31, line 1-22; page 31, line 30 - page 32; page 33, line 12-30; page 36, line 11-19; example 8), however, the specific combination is not disclosed and therefore, the subject matter of claims 1-55 is considered to be novel.

2.2.2 The present application does satisfy the criterion set forth in Article 33(2) PCT

because the subject-matter of claims 1-71 is new in respect of the cited prior art as defined in the regulations (Rule 64(1)-(3) PCT).

2.3 INVENTIVE STEP (Art. 33(3) PCT)

- 2.3.1 For inventive step analysis of claim 1,48,55,56,58, D2 is considered to represent the most relevant state of the art and discloses immunogenic compositions comprising a biological molecule from *Neisseria* in combination with transferrin binding protein TbpA or TbpB and their use as a vaccine to treat or to prevent *Neisserial* infections (see abstract and page 2, line 12 - page 3, line 2; page 55, line 1-16). The subject-matter of claims 1,48,55,56,58 differs in that the immunogenic composition comprises Hsf like protein in combination with transferrin binding protein.
- 2.3.2 The problem to be solved by the subject matter of claims 1,48,55,56,58 may therefore be regarded as the provision of an alternative combination with transferrin binding protein as immunogenic composition. The solution would be the combination of Hsf like protein and transferrin binding protein.
- 2.3.3 This solution is considered as involving an inventive step (Article 33(3) PCT). Although D2 mentions the use of transferrin binding protein in combination with other proteins in a vaccine composition and D3 describes the use of Hsf like protein in a vaccine composition (see abstract; claims 1-11,29,31-33). No incentive or suggestion can be found in the prior art concerning the combination of transferrin binding protein and Hsf like protein, mainly bearing in mind the synergistic effect of the presence of both proteins on the production of bactericidal antibodies (see examples).
- 2.3.4 A genetically engineered bacterial strain of claim 60 is considered to be inventive because incentive or suggestion can be found in the prior art for making such a bacterial strain and because it would not be obvious for the person skilled in the art to make this specific bacterial strain.
- 2.3.5 The methods of claims 61-65 for making the novel and inventive immunogenic or vaccine compositions of claims 1-55 are inventive. Processes which themselves would not involve an inventive step are nevertheless patentable insofar they provide a novel and inventive product (Guidelines CIV,9.12).

- 2.3.6 For inventive step analysis of claim 66-71, D3 is considered to represent the most relevant state of the art and discloses antibodies against Hsf like protein and their use for the prevention or treatment of Neisseria infection. (see abstract and claims 20,21,30). The subject-matter of claims 66-71 differs in that the Hsf like protein antibodies are used in combination with transferrin binding protein antibodies.
- 2.3.7 The problem to be solved by the subject matter of claim may therefore be regarded as the provision of an alternative antibody composition. The solution would be a composition comprising a combination of Hsf like protein antibodies and transferrin binding protein antibodies.
- 2.3.8 This solution is considered as involving an inventive step (Article 33(3) PCT) because no incentive or suggestion can be found in the prior art concerning the combination of Hsf like protein antibodies and transferrin binding protein antibodies also bearing in mind the unexpected synergistic effect of the presence of both antibodies on bactericidal activities.
- 2.3.9 The present application does therefore satisfy the criterion set forth in Article 33(3) PCT and the subject-matter of claims 1-71 does involve an inventive step (Rule 65(1)(2) PCT).